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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/886,296
Filing Date: June 21, 2001
Appellant(s): TARARA ET AL.

Guy Tucker
Registration No. 45,302
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 22, 2010 appealing from the Office action mailed June 22, 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct. The maintained rejections are:

The rejection of claims 57, 59-80, and 82-102 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 57, 59-77, 80, 82-100 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Papahadjopoulos et al

(Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by 5,776,488.

The rejection of claims 78 and 101 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by 5,776,488 in further view of Igarashi et al (4201774).

The rejection of claims 79 and 102 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by 5,776,488 in further view of Benson et al (5,006,343).

The rejection of claims 57, 59-80, 82-102 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 8-9, 11-15, 17, 19-25, 29-32, 53-55, 57-62, 64-66, 67-89 of Application No. 09/851226 (now US Patent 7,442,388).

The rejection of claims 57, 59-80, 82-102 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-7, 9-10, 46-50, 54-57, 59, 61-67, 69-70, 74-77, 79-90 of copending Application No. 09/568818.

The rejection of claims 57, 59-80, 82-102 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 1-15, 19-22, 37-49, 52-64, 67-79, 82-83, 94, and 102 of copending Application No. 10/750934.

The rejection of claims 57, 59-80, 82-102 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27, 32-39 of copending Application No. 10/982191.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

The rejection of claims 57, 59-77, 80, 82-100 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Unger (6,120,751) as evidenced by 5,776,488.

The rejection of claims 78 and 101 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) as evidenced by 5,776,488 in further view of Igarashi et al (4201774).

The rejection of claims 79 and 102 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) as evidenced by 5,776,488 in further view of Benson et al (5,006,343).

The rejection of claims 57, 59-77, 80, 82-100 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) respectively as evidenced by 5,776,488.

The rejection of claims 78 and 101 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) as evidenced by 5,776,488 in further view of Igarashi et al (4201774).

The rejection of claims 79 and 102 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) as evidenced by 5,776,488 in further view of Benson et al (5,006,343).

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

A.) Hanes et al (US 5,855,913)

B.) Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491)

C.) Mori et al (US 5,776,488)

D.) Igarashi et al (US 4,201,774)

E.) Benson et al (US 5,006,343).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A.) Claims 57, 59-80, and 82-102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 57, 80, and their dependent claims recite the limitation, "...wherein the particulate microstructures comprise **greater than about** 50% phospholipid." "Greater than" is a minima and all possible values above 50% are encompassed. "About" indicates a range centered on the recited value. In this case, "about" indicates both values above and below 50%. Therefore, what values are included in the range "greater than about 50% phospholipid" cannot be determined.

B.) Claims 57, 59-77, 80, and 82-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by US 5,776,488. Note US '488 is only relied upon to show the inherent property claimed in claims 72 and 95.

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3 microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC (phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the

envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allow the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid and is present in an amount of 62.8 wt.% and 89.1 wt.% in Table 4 of Hanes (column 18, lines 35-50). The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) and the

polyester may also have charged or functionizable groups such as amino acids. Other polymers taught are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Further, the particles may be formed into microspheres by various methods including but not limited to **coacervation (note a coacervate is a spherical aggregation of lipid molecules)**, interfacial polymerization, etc. (note col. 6). Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25.

Hanes et al do not teach the use of calcium in the structural matrix.

Papahadjopoulos et al teach adding calcium to fuse phospholipids including the phospholipids taught by Hanes into larger vesicles. The reference teaches small vesicles with a size of 200-500 A in diameter can be made into bigger vesicles of a size of 0.2-1 micron. The reference teaches using calcium to form the desired size of the vesicle. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Papahadjopoulos and utilize calcium. One would be motivated to do so with the expectation of similar results

since Hanes teaches the use of phospholipids only to form the particles and Papahadjopoulos teaches the use of calcium provides the desired vesicle size. Therefore, a skilled artisan would have been motivated to use the desired concentration of calcium to provide the desired lipid vesicles size. Note that the amount of calcium used provides the desired size as taught by Papahadjopoulos. Papahadjopoulos teaches forming bigger vesicles of a size of 0.2-1 microns in diameter and applicant claims a size of 1-30 microns.

With regard to the claims 4-5 (porosity), claims 6-7 (pore size), and claim 13 (shell thickness), although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It should be noted that the examiner has provided a

rationale as to why Hanes's particle would have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters is considered prima facie obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density to determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

C.) Claims 78 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by 5,776,488 in further view of Igarashi et al (4201774).

The detailed teachings of Hanes and Papahadjopoulos have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition.

Hanes does not teach the specific use of aminoglycoside antibiotic.

Igarashi et al teaches aminoglycoside antibiotics for the treatment of gram-positive and gram-negative bacteria.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant medicament in Hanes' composition. One would be motivated to do so since the instant antibiotics treat gram-positive and gram-negative bacteria and depending on the patient's requirement, the appropriate drug is used. One would have expected similar results since Hanes teaches the suitability of antibiotics as the active agent. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

D.) Claims 79 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by 5,776,488 in further view of Benson et al (5,006,343).

The detailed teachings of Hanes and Papahadjopoulos have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition.

Hanes does not teach the specific use of fungicides.

Benson et al teach pulmonary administration of active agents to treat pulmonary diseases. Suitable drugs that may be administered for lung specific disease include fungicides. See column 10, lines 33-45.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a fungicide in Hanes et al's composition. One would be motivated to do so since Benson et al teach the use of array of medications including fungicides that are useful for treating lung diseases. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

E.) Claims 57, 59-80, and 82-102 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 8-9, 11-15, 17, 19-25, 29-32, 53-55, 57-62, 64-66, 67-89 of Application No. 09/851226 (now US Patent 7,442,388).

The instant application is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3,

and an aerodynamic diameter of less than 5 microns. The claims are also directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'226 is directed to a particulate composition comprising an active agent, a saturated phospholipid, and a polyvalent cation, wherein the ratio of the polyvalent cation to phospholipid is at least 0.05 and is sufficient high to increase the gel-to-liquid crystal transition temperature of the particles without the cation. Dependent claims are directed to calcium as the metal ion. Dependent claim is directed to a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to the same active agent insulin and growth hormones. Dependent claims are directed to a mass median diameter of 0.5-5 microns, an aerodynamic diameter of 0.5-5 microns, and a bulk density of less than 0.5 and 0.05 respectively. The phospholipid is selected from dipalmitoylphosphatidylcholine and disteroylphosphatidylcholine.

The instant application and '226 are different in that '226 is directed to the broad scope of the metal ion and the instant application is directed to the metal ion species calcium; however, '226 claims calcium in the dependent claims. Further, '226 claims the

amount of the cation to increase the gel to liquid transition temperature and the instant application does not recite any concentration of the cation. However, the manipulation of concentrations is considered to be prima facie obvious. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, the instant application and copending application have overlapping subject matter wherein both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

F.) Claims 57, 59-80, and 82-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-7, 9-10, 46-50, 54-57, 59, 61-67, 69-70, 74-77, 79-90 of copending Application No. 09/568818. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antifungals, insulin, etc. The phospholipid is selected from

dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

Copending independent claims 46, 59, and 82 are directed to a microparticle comprising an active agent and a metal-ion complex with a density as measured by He displacement is 0.5-2 g/ml. Calcium is one of the metal ion species claimed in a dependent claim. Dependent claims are directed to phospholipids and specifically selected from the group comprising "dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, and dimyristylphosphatidylcholine". Dependent claims are directed to the same active agents as claimed in instant application. Dependent claims are directed to an aerodynamic particle size of 0.5-7 microns. Dependent claims are directed to dry powder. Dependent claim are directed to a zwitterionic lipid.

The instant application and '818 are different in that firstly '818 independent claims do not recite a phospholipid; however the dependent claims further comprise phospholipids, more specifically, the instant phospholipids. Thus, the instant application and copending application have overlapping subject matter wherein both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion. Secondly, '818 is directed to the broad scope of the metal ion and the instant application is directed to the metal ion species calcium; however, '818 claims calcium in the dependent claims. Further, '818 is broadly directed to microparticles without claiming the density, the geometric diameter, pore size, etc.; however '818 encompasses the scope of the instant microstructures and the respective

properties, which is the narrower scope. Lastly, it should be noted with regard to instant claim 40, although '818 does not specifically claim "phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius", '818 does claim DPPC in the dependent claims and DPPC has a temperature of 42 degrees Celsius.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

G.) Claims 57, 59-80, and 82-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15, 19-22, 37-49, 52-64, 67-79, 82-83, 94, and 102 of copending Application No. 10/750934. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine,

dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'934 is directed to a pharmaceutical composition comprising particles comprising an active ingredient in a lipid matrix. The particles have a geometric diameter of less than 3 microns and a mass median diameter of less than 20 microns. Dependent claims are directed to a lipid selected from dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine. Dependent claims are directed to hollow, porous particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3. Dependent claims are directed to the particle further comprising a polyvalent cation and the specification defines the polyvalent cation as calcium, magnesium, and iron. Independent claim is directed to a specific active agent, amphotericin.

Copending application and instant application are different because '934's independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further comprising polyvalent metal ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

H.) Claims 57, 59-80, and 82-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 1-27, 32-39 of copending Application No. 10/982191. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'191 is directed to a pharmaceutical composition comprising active ingredient and a lipid wherein the gel to liquid crystal transition temperature of greater than 57 degrees Celsius. The dependent claims are directed to the lipid components selected from dipalmitoylphosphatidylcholine. Dependent claims further comprise a divalent cation, specifically calcium. Dependent claims are directed to composition in a dry powder form wherein the particles are hollow and porous particles. Dependent claims are directed to the particles having a geometric diameter of less than 20 microns. Dependent claims

are directed to the particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3.

Copending application and instant application are different since '934's independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further comprising polyvalent metal ions, specifically calcium ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

(10) Response to Argument

Rejection A.)

Appellant argues that the Examiner offers no reasoning as to why the language is indefinite in the present case. Appellant argues that the range of "about" would be clear to one of ordinary skill in the art from the context of the specification. As such, Appellant argues that the range of "greater than about" is also clear since it includes everything that is "about 50%" and everything that is greater than about. Appellant notes that a word search of US Patents issued in 2009 reveals that no fewer than 1257 patents include the expression "greater than about" in their claims. Accordingly, Appellant requests reversal of the rejection.

In response to Appellant's arguments, the Examiner notes limitations such as "greater than about" are unclear because they refer to both a range with a minima and a

range centered on the recited value. The Examiner acknowledges that in determining the range encompassed by the term "about", one must consider the context of the term as it is used in the specification and claims of the application. However, since the specification lacks a definition of “about” and Appellant has not fully explained how "about" is clear to one of ordinary skill in the specification, it is impossible to determine the metes and bounds of the ranges recited in the instant claims. The fact that other patents have been issued with the limitation “greater than about” has no merits on the pending prosecution of this case. Appellant failed to explain the prosecution history patents of these other patents and the circumstances in which other Examiners issued those claims. It is the position of the Examiner that Appellant must amend the claim limitations to individually recite "greater than" or "about" in order to overcome the pending rejection.

Rejection B.)

Appellant argues that Hanes does not disclose or suggest a particulate microstructure comprising greater than about 50% phospholipid. Instead, Hanes discloses particles that are either primarily polymeric or that are solely surfactant and drug. Additionally, Appellant argues that Paphadjopoulos and Mori do no make up for the deficiencies of Hanes. According to Appellant, Hanes teaches primarily polymeric particles and as such, one would not arrive at particles that are greater than 50% phospholipid. In the second embodiment of Hanes, Hanes teaches away from additional components by its use of solely and if there is no polymer in the particle, calcium-

polymer interactions discussed by Papahadjopoulos would not apply. Appellant argues that the Examiner has failed to establish that the teachings of Papahadjopoulos could be applied with a reasonable likelihood of success to Hanes. Appellant submits that they have unexpectedly found that its invention is particularly useful for delivering an active agent to the lungs in a reproducible manner.

In response to Appellant's arguments, it is the position of the Examiner that an ordinary skilled artisan would envisage and be able to make particulates comprising more than 50% phospholipid given the implicit teachings of Hanes and Papahadjopoulos. The Examiner directs Appellant's attention to example 2, column 11, lines 58-57 of Hanes, wherein the reference teaches spray-dried particles comprising 80 wt.% polymer and encapsulated 20 wt.% drug (testosterone). Since Hanes also teaches particles **that can consist solely of drug and surfactant** and that drug can be encapsulated within the surfactant (see column 10, lines 4-23), it would be within the skill of an artisan to substitute the 80 wt.% polymer for 80 wt.% surfactant in the drug encapsulated particles of Hanes' example 2. It should be noted that Hanes teaches two embodiments: one embodiment in which the particle is made of a polymer and surfactant to encapsulate a drug and a second in which the particle is made of solely of a surfactant to encapsulate a drug. One can easily envisage the use of either embodiment.

In addition to the implicit teaching of Hanes, Papahadjopoulos teaches that the structure of lipid vesicles depends on lipid concentration. Papahadjopoulos states that in a more concentrated lipid suspension, attractions between neighboring lamellae may

lead to the formation of planar multi-bilayers (see pg. 489). MPEP 2144.05 states, "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).* The amount of lipid is a result-effective variable because Papahadjopoulos clearly suggests that higher amounts of lipid can impart planar mulit-bilayers instead of multiple apposed bilayers. Therefore, it would be obvious to experiment with manipulating and optimizing the amount of lipid in the particulates of Hanes depending on the desired structure of the particulates. One would have been motivated to determine the optimal amount of lipid in order to best achieve the desired results. See *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).* As such, in light of Hanes' implicit teachings of phospholipid amount and the motivation given in Papahadjopoulos to optimize the lipid amount, it is the position of the examiner that the limitation, "wherein the particulate microstructures comprise greater than about 50% phospholipid" is taught by the combination of references.

Regarding Appellant's arguments that Hanes teaches away from polymers in its particles by the use of "solely drug and surfactant" in their disclosure, the Examiner notes that the vesicles of Papahadjopoulos are made solely of lipid and not polymer. Papahadjopoulos teaches adding calcium to fuse phospholipids including the phospholipids taught by Hanes into larger vesicles and therefore teaches an artisan of ordinary skill how to make the particles implicitly described in example 2 of Hanes. Hanes also does not exclude calcium from its particles. Hanes's context is directed to

excluding polymer and not excipients that facilitate the method of making the microstructure. Papahadjopoulos clearly teaches the use of counter ions such as calcium in the formation of a microstructure and Hanes teaches "Particles may be made using methods for making microspheres or microcapsules known in the art." (see column 6, lines 66-67).

The Examiner respectfully disagrees with Appellant that there is no motivation to combine Hanes with Papahadjopoulos. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Papahadjopoulos and utilize calcium. One would have been motivated to do so with an expectation of similar results since Hanes teaches the use of phospholipids to form particles and Papahadjopoulos teaches the use of calcium provides the desired vesicle size. Therefore, a skilled artisan would have been motivated to use the desired concentration of calcium to provide the desired lipid vesicle size.

Finally, regarding Appellant's argument of unexpectedly finding that the claimed invention is particularly useful for delivering an active agent to the lungs in a reproducible manner, Hanes teaches a plurality of particles used for delivering active agents to the lungs. Hanes teaches that the particles may be prepared using single and double emulsion solvent evaporation, spray drying, solvent extraction, etc and any other methods for making microspheres or microcapsules known in the art. Therefore, like the claimed invention, Hanes also teaches the delivery of an active agent to the lungs in a reproducible manner. According to MPEP 2145, a showing of unexpected results must be based on evidence, not just mere arguments or speculation. *In re Mayne, 104 F.3d*

1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997) (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome prima facie case of obviousness). Since Hanes teaches a plurality of particles that can be formed in a reproducible manner, Appellant's argument claiming unexpected results is not found persuasive.

Therefore, it is the position of the Examiner that the rejection over Hanes in view of Papahadjopoulos as evidenced by Mori should be maintained for the reasons stated above.

Rejection C.)

Appellant only argues that Igarashi does not cure the deficiencies of Hanes and Papahadjopoulos. Appellant believes that the claims are allowable for the reason that they depend from allowable claims.

The merits of Hanes and Papahadjopoulos have been discussed above and are incorporated herein. The rejection of Hanes in view of Papahadjopoulos is maintained and thus the dependent claims are not allowable. Igarashi is only relied upon to teach the instant aminoglycoside antibiotic as an active agent, which Appellant has not addressed.

Thus, it is the Examiner's position that Hanes in view of Papahadjopoulos and in further view of Igarashi renders the claims obvious.

Rejection D.)

Appellant did not present any arguments for this rejection.

Thus, it is the Examiner's position that Hanes in view of Papahadjopoulos, and in further view of Benson renders the claims obvious.

Rejection E.)-H.)

Appellant states that the provisional double patenting rejections will be addressed upon the indication of allowable subject matter. Appellant notes that they will file terminal disclaimers. Therefore, the rejections are maintained for the reasons stated above.

11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this Examiner's answer.

Respectfully submitted,

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Examiner, Art Unit 1611
4/21/10

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